associated folding pathways at multiple levels, from atomistic to coarse-grained representations. We validate our approach in folding studies of short helix-forming polyalanine peptides, as well as of a larger, helix-turn-helix subdomain of a viral scaffolding protein. Our analysis of local, site-specific formation of intra- and inter-chain interactions is a first step towards understanding the elementary stages of secondary and tertiary structure formation in the folding of large proteins, and it allows a direct comparison to data from recent infrared vibrational spectroscopy studies.

2919-Pos Board B24
Flow-Induced Beta-Hairpin Folding of the Glycoprotein Ib-alpha Beta-Switch
Xueqing Zou.
Flow-induced shear has been identified as a regulatory driving force in blood clotting. Shear induces beta-hairpin folding of the glycoprotein Ib-alpha (GPIb-alpha) beta-switch which increases affinity for binding to the von Willebrand factor, a key step in blood clot formation and wound healing. To explore the mechanism underlying the flow-induced conformational transition, we conducted altogether 2.1 microsecond molecular dynamics simulations of flow acting on the beta-switch of GPIb-alpha. Simulations sampling different flow velocities reveal that under flow, beta-hairpin folding is initiated by hydrophobic collapse, followed by interstrand hydrogen bond formation and turn formation. Adaptive biasing force simulations are employed to determine the free energy required for extending the unfolded beta-switch from a loop to an elongated state. Lattice and freely-jointed chain models illustrate how the folding rate depends on the entropic and enthalpic energy, the latter controlled by flow. The results reveal that the free energy landscape of the beta-switch has two stable conformations, loop and hairpin, imprinted on it. Normal flow prefers the disordered state; high shear flow prefers the ordered state, inducing thereby a transition between the two.

2920-Pos Board B25
Protein Flexibility Partitions the Effects of Energy Landscape Roughness Between Activation Energy and Internal Friction
Anna A. Rauscher, Zoltan Simon, Gergely J. Szollosi, Laszlo Graf,
Imre Derenyi, Andras Malnasi-Csizmadia.
The rate of protein conformational changes are usually not only limited by external but also internal friction, however, the origin and significance of this latter phenomenon is poorly understood. By investigating the internal friction during the activation of two trypsin mutants at various temperatures and external viscosities we have discovered that the temperature dependence of the internal friction shows an Arrhenius-like behavior. The characteristic energy of the Arrhenius formula, however, can change dramatically upon the replacement of a single amino acid at a hinge position (thereby affecting the flexibility of the protein), or by crossing a critical temperature. At the same time, the activation energy of the conformational transition also changes with a similar magnitude, but in the opposite direction. These observations shed light on the intricate interplay between the apparent internal friction and activation energy. Moreover, we have found that the more flexible a protein is the greater proportion of its activation energy is partitioned into internal friction. All these results have allowed us to come to the general conclusion that the different hierarchical levels of the roughness of the energy landscape along a conformational transition can be observed as either activation energy or internal friction depending on the degree of flexibility of the protein.

2921-Pos Board B26
Relationship Between Internal Friction and the Roughness of the Energy Landscape of Protein Conformational Changes
Anna Á. Rauscher, Zoltán Simon, Gergely J. Szöllősi, László Gráf,
Imre Derényi, Andras Malnasi-Csizmadia.
We constructed a quantitative model based on experimental data that describes the relationship between the roughness of the energy landscape, activation energy and internal friction of enzyme conformational changes. We investigated an interdomain conformational rearrangement, trypsinogen 4 activation using transient kinetic methods. The temperature and viscosity dependence of the rate constant of the conformational change was measured in order to determine the temperature dependence of its internal friction. To test the effect of flexibility on internal friction, glycine and alanine mutations at a single position of the hinge of the interdomain region were introduced. Internal friction showed an Arrhenius-like temperature dependence, the characteristic energy of which increased with the flexibility of the hinge.
We found that the activation energy, i.e. the height of the energy landscape, is partially converted into internal friction to an extent depending on the flexibility of the protein. We interpret this phenomenon using a model that assumes different hierarchical levels of roughness of the energy landscape.

2922-Pos Board B27
Predicting Sequence of Events upon Ligand Binding Using PMT Model: A Case Study of Adenylate Kinase
Gamze Gursoy, Hsiao-Mei Lu, Jie Liang.
Conformational transitions play a crucial role during the reaction cycle of many enzymes. In the case of adenylate kinase (AK), binding of ATP and AMP induces a conformational change where the closing of the LID and NMP domains over the core domain is followed by the phosphate transfer from ATP to ADP. This conformational change is rate-limiting for the enzymatic reaction, and AK is thought to be in equilibrium between open and close states. In this work, we studied the sequence of events along the conformational transition pathway. Using the Perturbation-based Markovian Transmission (PMT) model [Lu and Liang, PLOS Computational Biology, 2009], we study each of the 45 intermediate conformations available in PDB. We apply an initial perturbation on the binding domains of the enzyme, whose transmission is modeled as a Markovian Process. The dynamics of the probability flow is then computed by solving the Master Equation using a Krylov subspace method. From the landscape of time-evolving probability flow of all residues upon initial perturbation, we calculated the information entropy and related parameter for each residue. By analyzing time-dependent changes in entropy of residues located within or are in-contact with the LID/NMP domains, we predicted contacts that would break first for each conformation. Using the initial open state conformation only we are able to identify the next conformation along the conformation transition pathway with an average accuracy of 85% in predicted bond breakage We also predicted a set of critical residues with distinct dynamic behavior that are important in ligand binding.

2923-Pos Board B28
A Comprehensive Examination of the Contributions to Binding and Activation Entropies
Jie Cao, Arieh Warshel.
The elucidation of the role of entropic effects in enzyme catalysis and binding free energy is a problem of practical and fundamental interest. In order to address this problem it is essential to develop simulation methods capable of evaluating the entropic contribution to the overall free energy. Such an evaluation is useful for assessing temperature effects and exploring specialized options in enzyme design. In fact, the general ability to evaluate activation entropies of chemical reactions in solution has long been a challenge to computational chemists. Here we present what is probably the first microscopic evaluation of all of the relevant components to the relevant entropy, namely, configurational, polar solvation and hydrophobic entropies. All of these contributions are evaluated by the restraint release (RR) approach. In the case of binding entropies we found out major compensation effects in both the solvation and hydrophobic effect, and despite some overestimate, can provide very useful insight. Furthermore, exciting current use of our approach lead to the elucidation of the origin of the puzzling strong temperature dependence of the activation entropy in ADH. It is found that this effect does not reflect any dynamical factor, but rather the change in the polarization of the protein polar groups (plus water molecules) upon moving from the ground state to the transition state. This helps to resolve the long-standing question about the origin of the observed non linear Arrhenius plot.

2924-Pos Board B29
Structural Instability of the Active Site of T1 Lipase where Na^+-π Interaction is Replaced with Water-π Complex
Yohsuke Hagiwara, **Jiyoung Kang**, Masaru Tateno.
The cation-π interaction is one of the strongest noncovalent forces. However, its biological role has been unknown, since few structures containing cation-π interaction have been determined in biological systems. Matsumura, et al. determined the crystal strcture of T1 lipase and found interactions between Na^+ and the aromatic ring of Phe16 in the active site. However, this Na^+-π interaction remained to be discussed whether it really exists or not. To investigate structural stability of Na^+-Phe interactions, we performed molecular dynamics (MD) simulations of T1 lipase.It is well known that the current conventional force fields cannot estimate the cation-π interaction correctly, whereas *ab initio* calculations require huge computational costs for the MD simulations. Accordingly, we developed a novel scheme to calculate the interaction energy with a high accuracy compared with the CCSD(T) level, and with a low calculation cost compared with the force field calculations. The result of our calculations definitely showed that the large enthalpy gain of the Na^+-π interaction was required to preserve the catalytic core structure. Since experimental approaches could not dismiss the possible presence of water instead of Na^+ in the active site of T1 lipase, we also examined the effects of water by performing MD simulations. Our analyses revealed that the water-π complex was unstable and led to the collapse of the coordinated structure of the active site. Thus, we